

ARTICLE

Characterizing the exposure–response relationship of idecabtagene vicleucel in patients with relapsed/refractory multiple myeloma

Jamie N. Connarn¹ | Han Witjes² | Marielle van Zutphen-van Geffen² | Rik de Greef² | Timothy B. Campbell³ | Kristen Hege³ | Simon Zhou¹ | Manisha Lamba¹

¹Bristol Myers Squibb, Summit, New Jersey, USA

²Certara Strategic Consulting, Oss, The Netherlands

³Bristol Myers Squibb, San Francisco, California, USA

Correspondence

Manisha Lamba, Bristol Myers Squibb, S5 2154, 556 Morris Ave, Summit, NJ 07901, USA.

Email: manisha.lamba@bms.com

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Bristol-Myers Squibb

Abstract

Idecabtagene vicleucel (ide-cel; bb2121) is a B-cell maturation antigen–directed chimeric antigen receptor (CAR) T cell therapy approved for treatment of patients with heavily pretreated relapsed and refractory multiple myeloma. This analysis evaluated exposure–response (ER) relationships of ide-cel with key efficacy end points and safety events. Ide-cel exposure data were available from 127 patients treated at target doses of 150, 300, or 450 × 10⁶ CAR+ T cells from the phase II KarMMA study (NCT03361748). Key exposure metrics, including area under the curve of the transgene level from 0 to 28 days and maximum transgene level, were calculated using noncompartmental methods. Logistic regression models, using both linear and maximum response function of exposure on the logit scale, were evaluated to quantify observed ER trends, and modified by including statistically significant individual covariates in a stepwise regression analysis. There was wide overlap of exposures across the target doses. ER relationships were observed for the overall and complete response rates, with higher response rates associated with higher exposures. Model-based evaluations identified female sex and baseline serum monoclonal protein less than or equal to 10 g/L as predictive of a higher objective response rate and a higher complete response rate, respectively. ER relationships were observed for safety events of cytokine release syndrome requiring tocilizumab or corticosteroids. The established ER models were used to quantify the ide-cel dose–response, which showed a positive benefit–risk assessment for the range of ide-cel exposures associated with the target dose range of 150–450 × 10⁶ CAR+ T cells.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen–directed chimeric antigen receptor T cell therapy for treatment of patients with relapsed/refractory

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myeloma. In the phase II KarMMa study, an exposure–response (ER) relationship was observed in which higher exposure was associated with deeper response and longer progression-free survival.

WHAT QUESTION DID THIS STUDY ADDRESS?

The objective of this study was to perform a detailed ER analysis of ide-cel for key efficacy end points and safety events.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

ER relationships were observed for efficacy end points of overall response rate (ORR) and complete response rate, and for safety events of cytokine release syndrome requiring tocilizumab or corticosteroids. Dose–response models were developed and used to predict ORR and cytokine release syndrome at different target dose levels.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

It does not appear that dose adjustments are needed for covariates. These prognostic models can be leveraged to simulate the impact of different predictor variables in future studies of ide-cel.

INTRODUCTION

Multiple myeloma (MM) is a malignant cancer defined by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow.¹ Despite several approved therapies, including immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies, deep and durable responses are uncommon in patients with relapsed or refractory MM (RRMM).^{2–4} B-cell maturation antigen (BCMA) has been shown to be uniformly overexpressed in benign and malignant plasma cells from patients with MM.^{5–8}

Idecabtagene vicleucel (ide-cel; bb2121) is an immunotherapy consisting of autologous T cells genetically modified to express a chimeric antigen receptor (CAR) specific for BCMA. In the pivotal phase II KarMMa study (NCT03361748), ide-cel demonstrated an overall response rate (ORR) of 73% and complete response (CR) rate (CRR) of 33% in heavily pretreated patients with MM who received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, with a median follow-up of 13.3 months.⁹ At a median follow-up of 24.8 months, the ORR was 73% and the CRR was 33%.¹⁰ Response rates improved at higher doses; among those who received the target dose of 450×10^6 , the ORR was 81%; 39% achieved CR.¹⁰ The initial study analysis also reported an association between higher area under the curve of the transgene level from time of dose to 28 days post-infusion (AUC_{0-28}) and deeper response with longer progression-free survival (PFS) after 3 months of follow-up from the last infusion.¹¹

Ide-cel has received regulatory approval from the US Food and Drug Administration (FDA) and other health authorities, including the European Medicines Agency (EMA), Health Canada, Swissmedic, and Japan.^{12–16} The objective of this analysis was to evaluate exposure–response (ER) relationships of ide-cel with the KarMMa study primary end point ORR, key secondary end point CRR, and safety events to evaluate therapeutic potential across the dose range evaluated in the KarMMa study.

METHODS

KarMMa study design

Analyses used data from the KarMMa trial, whose clinical methods, primary end point (ORR), and key secondary end points and safety data have been published previously.¹¹ Of 140 enrolled patients with RRMM, 128 patients received a single infusion of ide-cel at target doses of 150 (+20%), 300 ($\pm 20\%$), or $450 (\pm 20\%) \times 10^6$ CAR+ T cells. All patients received lymphodepleting chemotherapy agents fludarabine ($30 \text{ mg/m}^2/\text{day}$) and cyclophosphamide ($300 \text{ mg/m}^2/\text{day}$) 3–5 days prior to ide-cel infusion. Efficacy analyses were based on the Independent Response Committee assessment according to International Myeloma Working Group Uniform Response Criteria for MM.¹⁷ KarMMa was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Guideline for Good Clinical Practice (ICH E6) after approval from local or independent institutional review boards or ethics

committees at participating sites. Written informed consent was obtained from all patients.

Cellular expansion

Pharmacokinetics (PK) of ide-cel cellular expansion were described by the time course of transgene copies per microgram of genomic DNA as measured by a validated quantitative polymerase chain reaction assay.¹⁸ PK samples were collected at screening; days 2, 4, 7, 9, 11, 14, and 21; months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, and 24, or end of study, CR, or at progressive disease. The PK analysis population was defined as all patients who received at least one ide-cel infusion and had evaluable transgene level (i.e., at least one measurable timepoint).

Noncompartmental analyses of pharmacokinetics

Key exposure parameters (maximum transgene level [C_{\max}] and AUC_{0-28}) were calculated using noncompartmental methods. Observations that were below the lower limit of quantification were set to zero, and this value was used in the derivation of the AUC. Additionally, if an end time for the AUC calculation (day 28) was within the range of the data but did not coincide with an observed data point, then a logarithmic interpolation was done to estimate the corresponding concentration. If an end time occurred after the last numeric observation (i.e., not “missing” or “below quantification limit”) and terminal elimination rate constant (λ_z) was estimable, λ_z was used to estimate the corresponding concentration.

ER modeling

ER relationships of ide-cel were evaluated with multiple efficacy end points, including ORR and CRR, as well as safety events, including cytokine release syndrome (CRS), CRS that required concomitant medication with tocilizumab (CRS requiring tocilizumab), and/or corticosteroids (CRS requiring steroids), grade greater than or equal to 3 CRS, investigator-identified neurotoxicity (iiNT) that required corticosteroids, grade greater than or equal to two iiNTs, and cytopenias (neutropenia and thrombocytopenia with first recovery or last laboratory value at month 1 showing < grade 3). ER modeling was performed when all patients had greater than or equal to 3 months of PK follow-up after the last ide-cel infusion. Patients were included in the ER analyses when individual PK data and efficacy or safety data were available.

An initial graphical evaluation was performed to identify potential ER relationships. Descriptive statistics of the quartile of each of the exposure parameters were tabulated. For each end point, stacked bar graphs were created, which summarized the proportion of responders by exposure quartile for each of the PK/exposure parameters (C_{\max} and AUC_{0-28}). Based on these evaluations, candidate ER models were selected for model-based evaluations as described below. For the efficacy and safety end points for which the graphical evaluations indicated the potential presence of an ER relationship, the probability of the response in patient i (P_i) was described by a binary logistic regression model:

$$\text{logit}(P_i) = \log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_1 AUC_i$$

β_0 and β_1 represent the intercept and the linear effect of exposure on the probability of response on the logit scale, respectively, and AUC_i represents the predictor effects of AUC_{0-28} .

In case a statistically significant ER relationship was detected, potential effects of (additional) covariates on the probability of response were evaluated in the following ER model:

$$\text{logit}(P_i) = \log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_1 AUC_i + \beta_2 COV_i$$

β_2 represents the covariate effect size (COV_i) on the probability of response on the logit scale. Response rates on the probability scale were obtained by the inverse logit transform of the predicted logits.

If data allowed, a sigmoid maximum effect (E_{\max}) ER relationship on the logit scale was evaluated to improve the characterization of the ER relationships.

$$\text{logit}(P_i) = \log\left(\frac{P_i}{1-P_i}\right) = E_0 + \frac{(E_{\max} - E_0) \times AUC_i^H}{(EC_{50}^H + AUC_i^H)} + \beta_2 COV_i$$

E_0 is the response at zero exposure, E_{\max} the maximum response, EC_{50} the exposure to achieve half of E_{\max} , H the Hill coefficient reflecting the steepness of the E_{\max} relationship, and COV_i individual values of statistically significant covariates. Compared with the linear logistic regression model, the sigmoid E_{\max} model allows a maximum response rate lower than 100% at maximum exposure.

Covariate evaluation

Covariates considered for evaluation included baseline demographics, disease factors, pre-infusion variables, and

target dose (Table 1). Evaluation of covariates as predictors of safety or efficacy was carried out in a two-step process. First, univariate screening was performed in which the covariate effect on the response was tested in a linear logistic regression model including the covariate and exposure as predictors. Covariates were evaluated on the intercept only in the logistic model. Then, the covariates which were significant at a level of $p < 0.05$ in univariate analysis were subjected to an iterative forward addition and backward elimination model selection strategy. During the forward inclusion step of the stepwise covariate selection process, statistical significance of a covariate was evaluated at a 0.05 significance level. Covariates were included in the model when associated with a p value less than 0.05. Subsequently, the least significant covariate was eliminated in a backward deletion procedure until no more nonsignificant covariates were left in the model ($p > 0.01$). The p values were obtained with the likelihood ratio test.

Model evaluation

The developed ER models were evaluated by graphically superimposing model predictions on the observed data. Specifically, the models were evaluated by plots showing the model-predicted response rates compared with the observed response rates by exposure quartile. The predicted logistic regression curve and the observed response rate in each quartile of exposure (along with the associated 95% confidence intervals) were plotted to assess the overall goodness of fit of the models.

Simulations of dose–response

Dose–response simulations were used to predict ORR, CRR, and rates of CRS requiring tocilizumab and CRS requiring steroids at target doses of 150, 300, and 450×10^6 CAR+ T cells. Dose proportionality of AUC (linear effect of dose on AUC) was assumed to infer individual patient AUCs at each of the three ide-cel target dose levels from the AUC value estimated at the administered dose level. Thus, all patients had one calculated AUC at the administered CAR+ T cell dose and three predicted AUCs at the three target doses. The observed and predicted AUCs at target dose were identical only if the actual dose was equal to the target dose (i.e., actual dose equal to 150, 300, or 450×10^6 CAR+ T cells). The established ER relationship was then used to calculate the individual probabilities of response based on AUC. The sum of the individual probabilities across the doses characterized the dose–response relationship for the doses of interest.

Software

The analysis datasets were created using SAS version 9.4 (SAS Institute). The noncompartmental evaluation that formed the basis for the exposure metrics was calculated using Phoenix WinNonlin version 8.1. The PK characterization, ER evaluations, and ER simulations were performed in R version 3.5.1 (R Foundation for Statistical Computing). NONMEM (nonlinear mixed-effect modeling) software version 7.4 was used for covariate selection

TABLE 1 Covariates considered for evaluation^a

Baseline demographic factors	Disease factors	Pre-infusion variables	Target dose
Age ^b	Number of prior MM regimens	Tumor burden	150×10^6 CAR+ T cells
Weight	Last prior MM therapy	Urine M-protein	300×10^6 CAR+ T cells
Body surface area	Bridging therapy	Serum M-protein	450×10^6 CAR+ T cells
Race	Extramedullary disease	Ferritin ^c	
Sex	ECOG PS	Soluble BCMA ^{c,d}	
Ethnicity	Prior HSCT	Free light chain ^c	
	Type of lymphodepleting regimen	IL-6 ^c	
	Disease status (refractory vs relapse)	IL-15 ^c	
	Concomitant medication to manage CRS	TNF- α ^c	
		Anti-drug antibody status	

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; MM, multiple myeloma.

^aFor assessment of categorical variables, categories were combined if $< 10\%$ of participants fell into each category, and covariates missing for $> 10\%$ of patients were excluded from the analysis.

^bContinuous and binned by < 65 versus ≥ 65 years.

^cMeasured in serum.

^dBaseline and idecabtagene vicleucel pre-infusion.

and was run under PsN (Perl-speaks-NONMEM) version 4.8.1 (ICON Development Solutions).

RESULTS

In the KarMMa trial, 128 patients received ide-cel treatment. Ide-cel was administered at the target doses of 150, 300, and 450×10^6 CAR+ T cells to 4, 70, and 54 patients, respectively.¹¹ Among treated patients, the median age was 61 years (range, 33–78 years). Patients had received a median of six prior anti-myeloma therapies; a total of 108 (84%) patients were triple-class refractory (to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody) and 33 (26%) were penta-refractory. A total of 112 (88%) patients received bridging therapy.¹¹

PK analyses and graphical evaluation of ER relationships

At the data cutoff (April 19, 2019), which provided greater than or equal to 3 months of PK follow-up after ide-cel infusion, 127 of 128 patients had measurable C_{\max} values and

were included in the analysis population (Table 2); one patient died on day 4 and had no evaluable PK data. Data from 125 of these 127 patients were available for determination of AUC_{0-28} ; two patients did not have 1 month of post-infusion follow-up due to early discontinuation.

The key PK metrics (C_{\max} and AUC_{0-28}) showed a high degree of correlation (pairwise correlation coefficient = 0.93; Figure 1). Due to this high correlation, the remaining ER analyses focused on AUC_{0-28} .

Given the right-skewed distribution of AUC_{0-28} (Figure 1), the exposure parameter was natural log-transformed for the ER evaluations of the end points. As previously shown for CRR,¹¹ initial graphical evaluation revealed ER relationships among $\log(AUC_{0-28})$ quartiles and ORR, CRS requiring tocilizumab, and CRS requiring steroids (Figure 2). The proportion of patients who achieved overall response (OR), and the proportion who experienced CRS requiring tocilizumab, showed substantial increase from first AUC quartile (Q1) to second (Q2), and further increased from Q2 to third quartile (Q3) for OR. The proportion of patients who experienced CRS requiring steroids increased gradually from Q1 to Q3. Overall, the graphical analyses suggest that the ER relationships were less impacted by higher exposure quartiles,

TABLE 2 Number of patients in analysis data per target dose level for each exposure parameter

Parameter	Target dose ($\times 10^6$ CAR+ T cells)			Total $N = 128^a$
	150 $N = 4^a$	300 $N = 70^a$	450 $N = 54^a$	
C_{\max}	4	69	54	127
AUC_{0-28}	4	68	53	125

Abbreviations: AUC_{0-28} , area under the curve of the transgene level from time of dose to 28 days post-infusion; CAR, chimeric antigen receptor; C_{\max} , maximum transgene level.

^aAs reported in the KarMMa study phase II publication.¹¹

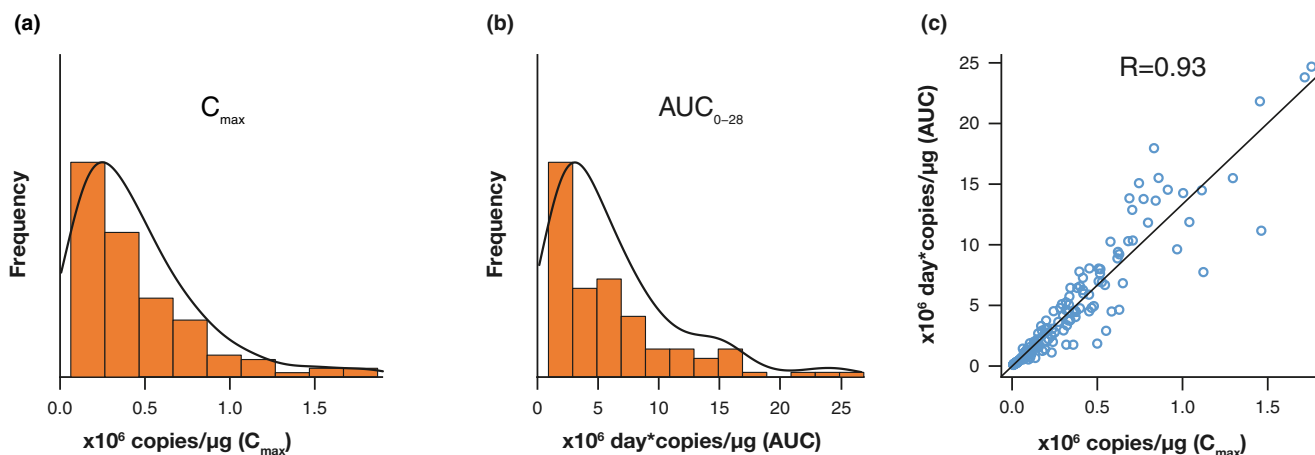


FIGURE 1 Correlation of C_{\max} and AUC_{0-28} . (a) C_{\max} , (b) AUC_{0-28} , (c) correlation plot; symbols refer to individual parameter estimates and solid black line shows linear regression. AUC_{0-28} , area under the curve of the transgene level from time of dose to 28 days post-infusion; C_{\max} , maximum transgene level; day*copies/μg, exposure as a function of time

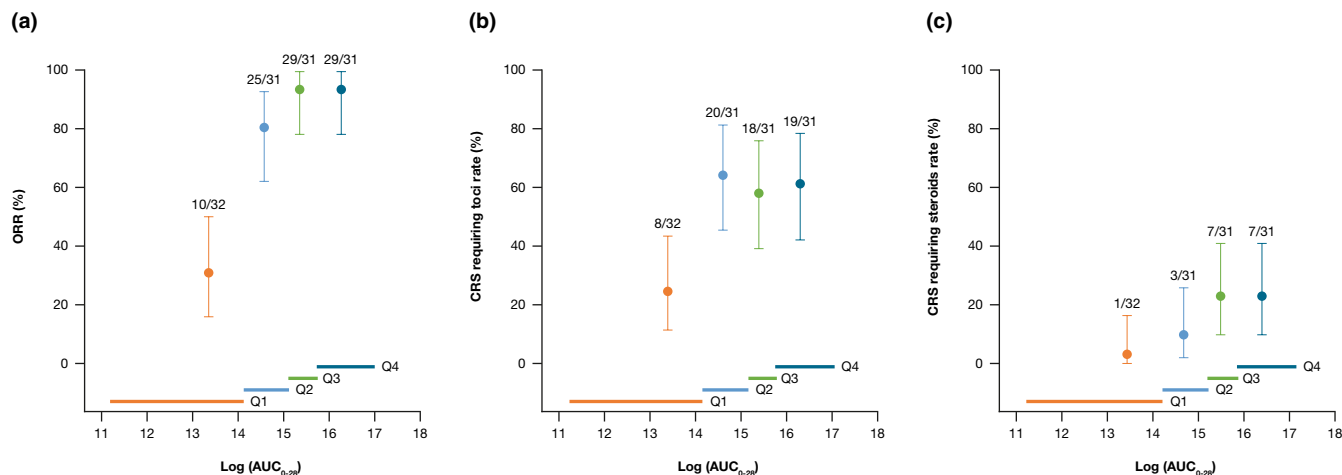


FIGURE 2 Graphical evaluation of ER relationship versus log(AUC₀₋₂₈). Observed (a) mean ORR, (b) mean CRS requiring tocilizumab, and (c) mean CRS requiring steroids, with associated 95% confidence interval for quartiles of log(AUC₀₋₂₈). Error bars are plotted at the median log(AUC₀₋₂₈) of each quartile. Horizontal lines represent log(AUC₀₋₂₈) ranges of each quartile. The numbers above the error bars (x/y) represent the number of patients who achieved the response (x) and the total number of patients (y) within each of the quartiles. AUC₀₋₂₈, area under the curve of the transgene level from time of dose to 28 days post-infusion; CR, complete response; CRS requiring steroids, cytokine release syndrome requiring medication with corticosteroids; CRS requiring tocilizumab, cytokine release syndrome requiring medication with tocilizumab; ER, exposure-response; ORR, overall response rate; Q, quartile

and primarily driven by the lowest exposure quartile. No ER relationships were observed for the safety events of grade greater than or equal to 3 CRS, iiNT (either grade ≥ 2 or requiring steroids), and cytopenias (Figure S1); however, it should be noted that a limited number of patients experienced these safety events (within the ER analysis population, grade ≥ 3 CRS [$n = 5$], iiNT grade ≥ 2 or requiring steroids [$n = 10$ and 9 , respectively], thrombocytopenia [$n = 37$], and neutropenia [$n = 41$]).

Logistic regression evaluation and model selection

To characterize the graphical trends observed, logistic regression evaluations were performed. Both a linear logistic model and a sigmoid E_{\max} logistic model were evaluated. For ORR, a sigmoid E_{\max} model fit the data best and was selected as the final model (Figure 3a). Sex was identified as a statistically significant covariate using the stepwise covariate selection method and indicated that the ORR was higher for women than men ($p = 0.003$); therefore, sex was included as a covariate in the final model for ORR.

For CRR, the Hill coefficient in the E_{\max} model could not be estimated and was fixed to 1 (Figure 3b), therefore effectively reducing the sigmoid E_{\max} model to a standard E_{\max} model. Overall, a similar fit was observed between the linear and standard E_{\max} model; however, because the residual standard error of the model parameter estimates was much higher for the E_{\max} model compared with the

linear model, the linear model was selected as the final model. The stepwise covariate selection indicated that CRR was higher for patients whose baseline serum monoclonal (M) protein (dichotomized by >10 g/L vs. ≤ 10 g/L) was less than or equal to 10 g/L ($p < 0.001$).

For CRS requiring tocilizumab, the sigmoid E_{\max} model plateaus at medium exposure levels, in line with the trend of observed rates, whereas the ER curve of the linear model continues to increase at medium and high exposures, in contrast to observed rates (Figure 3c). Therefore, the sigmoid E_{\max} model was selected as the final model to characterize the ER relationship for CRS requiring tocilizumab. The selection was confirmed by a lower Akaike information criterion score for the sigmoid E_{\max} model compared with the linear model (81.0 vs. 83.0, respectively). No statistically significant covariate effects on probability of CRS requiring tocilizumab were identified with the stepwise covariate selection procedure. Hence, no covariates were included in the final CRS requiring tocilizumab model.

For CRS requiring steroids, the ER relationship was fitted for a linear model only, as an E_{\max} model could not be fitted to the CRS requiring steroids endpoint (Figure 3d). Thus, the modeled ER relationship suggested a continued increase in CRS requiring steroids at high exposures, which appears to contrast with the identical observed CRS requiring steroids rates for Q3 and Q4. Despite its inability to describe this apparent plateau in observed CRS requiring steroids rates at Q3 and Q4 exposures, the model was selected as final because it showed an adequate performance overall in characterizing the ER across the four

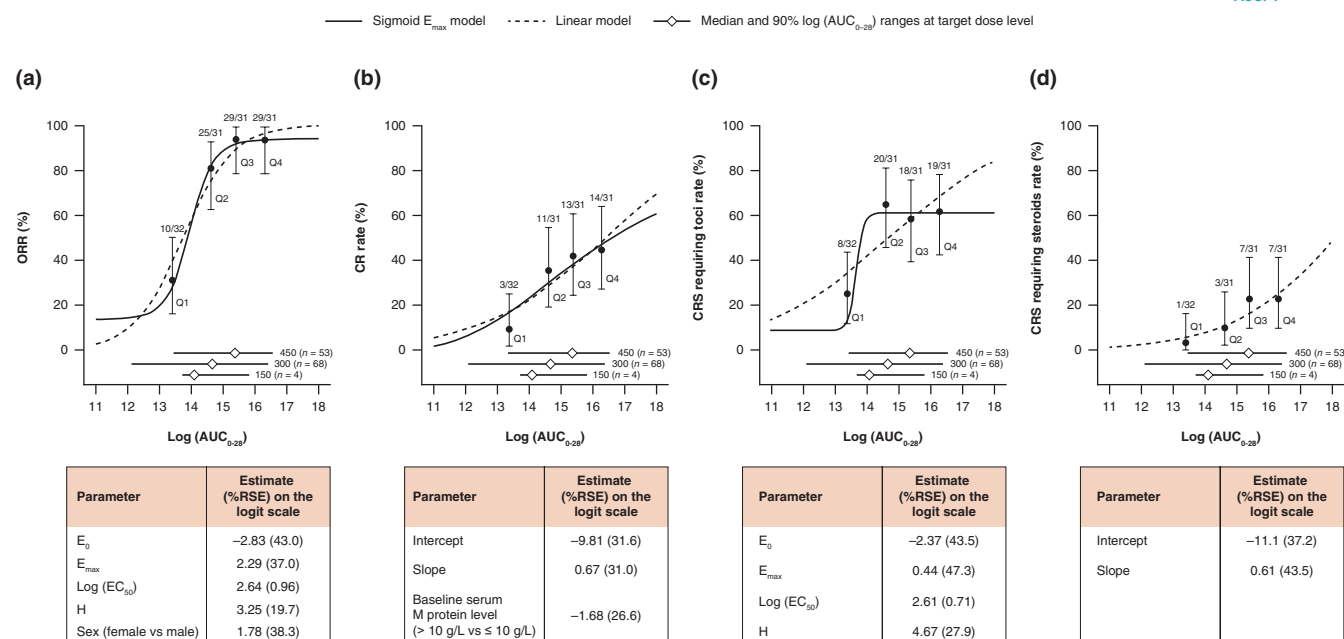


FIGURE 3 Final model predictions for (a) ORR, (b) CRR, (c) CRS requiring toci, and (d) CRS requiring steroids. Solid and dashed lines show the model-predicted ER relationship based on the sigmoid E_{\max} model and the linear model, respectively. Horizontal lines with diamonds represent medians and 90% log(AUC_{0-28}) ranges at each target dose level ($\times 10^6$ CAR+ T cells), where n is the number of patients at each dose level. Horizontal lines show the ranges of exposures associated with each of the quartiles. The error bars represent the observed mean ORR with associated 95% confidence interval for quartiles of log(AUC_{0-28}), and are plotted at the median log(AUC_{0-28}) of each quartile. The numbers above the error bars (x/y) represent the number of patients who achieved the response (x) and the total number of patients (y) within each of the quartiles. AUC_{0-28} , area under the curve of the transgene level from time of dose to 28 days post infusion; CR, complete response; CRS requiring steroids, cytokine release syndrome requiring medication with corticosteroids; CRS requiring toci, cytokine release syndrome requiring medication with tocilizumab; E_0 , response at zero exposure; EC_{50} , exposure to achieve half of E_{\max} ; E_{\max} , maximum response; ER, exposure-response; H, Hill coefficient reflecting the steepness of the E_{\max} relationship; ORR, overall response rate; Q, quartile; RSE, residual standard error

quartiles. There were no statistically significant covariates identified for inclusion in the final CRS requiring steroids model.

Model-predicted response rates

Finally, the established ER models for ORR and CRS requiring tocilizumab were used to simulate the dose-response ($n = 125$ patients per target dose) based on the final logistic regression models of ORR and CRS requiring tocilizumab (Figure 4). The established ER relationships for ORR, CRR, and safety indicate a positive benefit-risk assessment across the exposure range associated with the target doses of 150, 300, and 450×10^6 CAR+ T cells. Although the model predicted a lower mean ORR at the target dose of 150×10^6 CAR+ T cells (59.7%) compared with the two higher target doses (72.7% and 78.3% for 300 and 450×10^6 CAR+ T cells, respectively), the predicted activity at the low end of the target dose range is considered clinically meaningful in this highly refractory

patient population. Similarly, the predicted mean CRS requiring tocilizumab rates were 43.2%, 51.1%, and 53.9% at doses of 150, 300, and 450×10^6 CAR+ T cells, respectively.

Dose-response model external validation

To validate the dose-response model, predictions from the models based on the KarMMa data were compared with observed data from patients treated in CRB-401, a phase I, multicenter, two-part dose escalation and dose expansion study of ide-cel for adults with relapsed/refractory MM.¹⁸ At the target doses of 150 and 450×10^6 CAR+ T cells, the point estimate between the observed CRB-401 data and the model prediction was within 6% for ORR and CRR (Figure S2). A similar trend was observed for CRS requiring steroids, where the observed CRB-401 data and model prediction had similar point estimates. The observed rates of CRS requiring tocilizumab from CRB-401 were considerably lower than predicted by the KarMMa-based ER model.

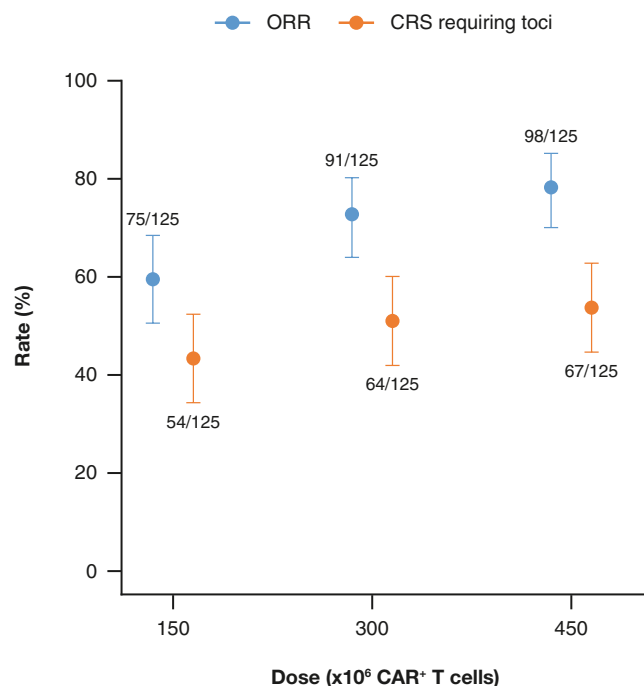


FIGURE 4 Model-simulated ORR and CRS requiring tocilizumab response by target CAR⁺ T cell dose level. Error bars represent the predicted mean and 95% confidence intervals of ORR (blue) and CRS requiring tocilizumab (orange) at each dose level. The numbers at the error bars (x/y) represent the predicted number of patients who achieved the response (x) and the total number of patients (y) for ORR (blue) and CRS requiring tocilizumab (orange) at each dose level. CAR, chimeric antigen receptor; CRS requiring tocilizumab, cytokine release syndrome requiring medication with tocilizumab; ORR, overall response rate

DISCUSSION

ER analyses are particularly important for adoptive cell therapies, where proliferation of the drug product occurs within the patient and as a result that the relationship between dose and exposure may vary. In addition, CAR T cell therapies are typically delivered as a single infusion, leaving less opportunity for adjusting exposure compared with conventional drugs involving multiple administrations.¹⁹ Both dose–response¹¹ and ER relationships were observed for ide-cel. The ER relationships were stronger than the dose–response relationships. It should also be noted that, unlike ER evaluations for drugs, exposure parameters for cellular therapies represent the initial response to the CAR⁺ T cell product, which is determined by the fitness and quality of the CAR⁺ T cells. For example, a preclinical study demonstrated that CAR T cells generated from patients with clinical response show more robust expansion and prolonged survival.²⁰ If cellular proliferation is adequate, then the ER relationship can further characterize the link between cellular expansion and clinical response. Previous reports of CD-19-targeted

CAR⁺ T therapies in B-cell acute lymphoblastic leukemia showed that responders had higher cellular expansion compared with nonresponders; however, analyses showed similar response rates across all dose quartiles.²¹ Further modeling of cellular kinetics showed no relationship between CAR⁺ T cell dose and exposure.²² Studies of multiple CAR⁺ T cell therapies have reflected this trend, with exposure more likely to predict response than dose.^{23,24} In the KarMMA trial, previously reported ER analyses revealed that patients in the lowest quartile (Q1) of exposure had the shortest PFS compared with those in the upper three quartiles of exposure.¹¹ Patients in Q1 had PFS of 3 months, compared with PFS of 8 months in patients in Q2-4. This prior analysis also showed a high overlap in exposure between the three target doses, outlined by the relative contribution of each of the quartiles for AUC_{0–28} to the AUC distribution per target dose. However, in general, with increased target dose, a greater percentage of patients were in Q3 and Q4 of the overall AUC distribution. The target dose of 450 × 10⁶ CAR⁺ T cells made the largest relative contribution to the highest exposure quartile (34% of the patients treated with this dose were found in Q4) and the smallest relative contribution to the lowest quartile (15% of the patients treated with this dose were found in Q1).¹¹

In this in-depth analysis using data from KarMMA, ER relationships were observed across the target ide-cel dose range of 150–450 × 10⁶ CAR⁺ T cells. ER evaluations provide a foundation for data integration and analyses through development of prognostic models that link cell expansion metrics with observed clinical response and safety events. Such prognostic models could also be leveraged for simulations of different predictor variables, including dose or patient factors.^{25–27}

In the logistic regression modeling of ORR, the sigmoid E_{\max} model was selected, and sex was identified as a statistically significant covariate, where women had a higher ORR compared with men. Characterization of sex on clinical outcomes in MM represents a challenge. In a recently reported epidemiologic analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results database and MM Research Foundation's CoMMpas dataset, Derman et al. have reported more favorable PFS and overall survival outcomes for women than men.²⁸ In contrast, an analysis of results from the Myeloma XI study showed important differences in MM biology, but not in clinical outcomes, based on sex.²⁹ In that study, newly diagnosed patients with MM (both transplant eligible and ineligible) were randomized to cyclophosphamide/dexamethasone and lenalidomide or thalidomide induction, followed by either cyclophosphamide/bortezomib/dexamethasone consolidation or no treatment for suboptimal responders, or autologous stem cell transplantation (for

transplant-eligible patients) and lenalidomide or no maintenance therapy for responders.²⁹ Plausible mechanisms for sex-based differences in clinical outcomes for women has been ascribed to health-promoting behavioral adjustments, higher drug concentrations, and lower frequency of regulatory T cells. Higher frequency of regulatory T cells, as observed in men, has been associated with worsened outcomes.²⁸ In our study, we did not find an effect of sex on cellular expansion after adjusting for body weight.¹³ Furthermore, the improvement in ORR in women did not translate to improved CRR in our analyses. Confirmation of this sex effect in myeloma and exploration of the mechanism remain to be determined. The ER effect for ORR demonstrated that patients who responded to ide-cel had higher median AUC₀₋₂₈, which was consistent with CRB-401.¹⁸ However, the ORR model showed that this effect was not limited to cellular expansion, and included other covariates such as sex.

For CRR, a linear model was preferred over the sigmoid E_{\max} model. The stepwise covariate selection identified baseline serum M-protein level as a statistically significant covariate, where patients who had baseline M-protein levels less than or equal to 10 g/L achieved higher CRR. Serum M-protein is associated with disease burden,^{30,31} suggesting that patients with lower disease burden responded better to ide-cel. This agrees with previous findings showing high tumor burden is a negative correlate of CR to ide-cel in RRMM³² and that high tumor burden is associated with a lack of durable response to CD19-targeted CAR+ T cell therapy in large B-cell lymphoma.³³ The final CRS requiring tocilizumab and CRS requiring steroids models were described using a sigmoid E_{\max} model and linear model, respectively. For both of these safety end points, no statistically significant covariates were identified. Although sex and baseline serum M-protein levels were statistically significant covariates of ORR and CRR, respectively, adjusting the dose to correct for these covariates would have limited clinical implications because there was substantial overlap in the distribution of exposures at 150, 300, and 450 × 10⁶ CAR+ T cells.¹¹ Exposure appears to be higher in patients treated with tocilizumab or corticosteroids for CRS. However, it should be noted that these correlations may be driven through a safety ER, with higher exposures associated with an increased probability of the occurrence of CRS requiring any of these treatments, rather than representing a direct effect of these treatments on cellular expansion.

One limitation of this ER analysis is the small number of patients ($n = 4$) who were infused with the lowest target dose of 150 × 10⁶ CAR+ T cells. Therefore, predicted responses were externally validated against data from eight patients in the CRB-401 study who received the 150 × 10⁶ CAR+ T cell dose. Observed CRR, ORR, and

CRS requiring steroids from CRB-401 aligned closely with model predictions; however, CRS requiring tocilizumab rates were considerably lower in CRB-401 than in model predictions. This apparent model overprediction of CRS requiring tocilizumab rates in CRB-401 may be explained in part by differences in study population and dosing, as well as the evolution in clinical practice. The use of tocilizumab has evolved with increased understanding of the IL-6 inhibition mechanism to manage CRS,³⁴ leading to more frequent use in later studies. One covariate not included in these analyses is the quality and composition of the CAR+ T cell product. Previous studies of CD19+ CAR T-cell products have revealed that factors such as T-cell functionality, exhaustion, and subset composition correlate with expansion and clinical efficacy of CAR+ T products, and combined index of polyfunctional indicators with T-cell expansion measures has demonstrated improved association with ORR.³⁵⁻³⁷ These factors should also be considered when predicting responses in future CAR T-cell studies.

Finally, caution should be taken in assuming dose-dependent increases in cellular kinetic parameters. Although a general trend displayed increased cellular kinetic parameters across the three target doses, ide-cel is a living CAR+ T cell product that proliferates both during the manufacturing process and after administration to the patient, which contributes to high biological intersubject variability in exposures.

In conclusion, analysis and modeling of data from the phase II KarMMA study revealed statistically significant ER relationships for the efficacy end points ORR and CRR and for the safety events CRS requiring tocilizumab and CRS requiring steroids. The ER relationships were primarily driven by the lowest quartile of AUC. There were no statistically significant ER relationships for grade greater than or equal to 3 CRS, iINT, and cytopenias. The established ER models were used to predict dose-response relationships within the dose range used for ER model development from the KarMMA study. These established relationships provide a foundation for quantitative characterization between cell expansion parameters and clinical efficacy end points and safety events for patients with RRMM using BCMA-directed cellular therapies.

AUTHOR CONTRIBUTIONS

J.N.C., T.B.C., and M.L. wrote the manuscript. J.N.C., R.D.G., S.Z., K.H., and M.L. designed research. J.N.C., H.W., M.Z.G., R.D.G., K.H., and M.L. analyzed data. J.N.C. and M.L. contributed analytical tools.

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CONFLICT OF INTEREST

J.N.C. was an employee of and held equity in Bristol Myers Squibb until July 2021 and is currently an employee of and holds equity in Amgen. H.W. is an employee of Certara, Princeton, NJ, USA, contracted by Bristol Myers Squibb, NJ, USA for data modeling. M.Z.G. is an employee of Certara, Princeton, NJ, USA, contracted by Bristol Myers Squibb, NJ, USA, for data modeling. R.D.G. is an employee of Certara, Princeton, NJ, USA, contracted by Bristol Myers Squibb, NJ, USA for data modeling, and holds equity in Certara. T.B.C. is an employee of and holds equity in Bristol Myers Squibb, has received support for conference attendance and travel from Bristol Myers Squibb, and has patents planned, pending, or issued with Bristol Myers Squibb. K.H. is an employee of and holds equity in Bristol Myers Squibb, holds patents with Bristol Myers Squibb, and is on the board of directors for Mersana Therapeutics and Graphite Bio. S.Z. is an employee of and holds equity in Bristol Myers Squibb. M.L. is an employee of and holds equity in Bristol Myers Squibb.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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